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Sterne Kessler Goldstein & Fox
Suite 600
1100 New York Avenue NW
Washington, DC 20005-3934

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,512	SCHRIER ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-39* is/are pending in the application.

4a) Of the above claim(s) *19-21,24-33 and 36-39* is/are withdrawn from consideration.

5)☒ Claim(s) *15 and 22* is/are allowed.

6)☒ Claim(s) *16-18,23,34 and 35* is/are rejected.

7)☐ Claim(s)_____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group 1, Claims 15, 34, SEQ ID NO:2, in Paper No.13 is acknowledged and entered.

Claims 15-39 are pending in the instant application and Claims 19-21, 24-33, 36-39 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Claim 22 has been rejoined with group 1, claims 15, 34. Further, claims 16-21, 23, 35 has been rejoined with group 1, as species.

Group 1, Claims 15-18, 22-23, 34-35, are currently under prosecution, wherein claims 15-18, 22-23, 34-35 are examined only to the extent of the polypeptides of SEQ ID NOs:2 and SEQ ID Nos:11-12, because species SEQ ID NO:2 is free of prior art, and species SEQ ID NOs:11-12 have been rejoined with species SEQ ID NO:2. Prosecution is halted at species SEQ ID Nos: 11-12, because SEQ ID Nos: 11-12 are known in the art. Species SEQ ID Nos: 24-26 and claims 19-21 are withdrawn from consideration, as being drawn to non-elected species.

The traversal is on the following ground(s):

1) The restriction is improper under PCT rules 13.1 and 13.2 because the inventions are linked by the general concept of the CAMEL polypeptide, and a method of use of said polypeptide.

Further, the polypeptides of groups 2-6 are merely fragments of the full length CAMEL polypeptide of SEQ ID NO:2, and thus share a common sequence.

In addition, the polynucleotides of groups 7-12 encode the polypeptides of SEQ ID NO:2, 11, 12, 24-26 and thus share a common technical feature since they encode for either the full length CAMEL polypeptide of SEQ ID NO:2 or fragments thereof.

2) Applicant requests to rejoin claim 22 with group 1, because claim 22 is directed to a composition comprising the polypeptide of claim 15 (SEQ ID NO:2), which belongs to group 1.

3) The method of group 18, claim 36 shares a special technical feature with the method of claim 34, of group 1, which is inducing a CTL response using the polypeptide of SEQ ID NO:2. Further, the method claim comprising group 18 depends from and includes all the limitation of the product of group I and should be rejoined with group I according to *In re Ochiai*.

4) Concerning groups 13-17, 19-23, treating using fragments of the CAMEL polypeptide of SEQ ID NO:2 are linked by a single general inventive concept, since they are merely fragments of the CAMEL protein of SEQ ID NO:2.

Applicant asserts that the Examiner has not commented on why the claims of groups 24, and 25-29 do not form a single general inventive concept with the claims of group 1.

It is noted that after review and reconsideration, groups 2-6 and 13-17 have been rejoined with group 1, wherein each of the polypeptide sequences of SEQ ID Nos: 2, 11, 12, 24, 25, 26 and method of use thereof constitutes a species, and that only species SEQ ID NOs:2 and SEQ ID Nos:11-12 are examined for reasons set forth above. The new species requirement for the polypeptides of SEQ ID Nos: 2, 11, 12, 24-26, is proper

because According to PCT Rule 13.2 and to the guidelines in Section (f)(i)(A) of Annex B of the PCT Administrative Instructions, all alternatives to a Markush group must have a common property or activity. Although the polypeptides of SEQ ID Nos: 11, 12, 24-26 share a common property as belonging to CAMEL protein of SEQ ID NO:2, the polypeptides are not regarded as being of similar nature because all the alternatives do not share common property or activity. SEQ ID Nos: 2, 11, 12, 24, 25, 26 do not share the same or common structure and function.

Further, after review and reconsideration, claim 22 is rejoined with group 1.

Similarly, after review and reconsideration, the polynucleotides of groups 7-12 have been rejoined as one group, which is separate and distinct from the polypeptides of groups (1-6, 13-17), and each of the polynucleotides encoding each of the polypeptide sequences of SEQ ID Nos: 2, 11, 12, 24, 25, 26 constitutes a species. Similar reasons for species requirement of the polypeptides set forth above apply as well for the encoding polynucleotides thereof.

After review and reconsideration, group 18 is rejoined with groups 19-23, and an ex vivo method using each of the polypeptide sequences of SEQ ID Nos: 2, 11, 12, 24, 25, 26 constitutes a species.

After review and reconsideration, group 24 is rejoined with groups 25-29, and an ex vivo method using each of the polynucleotides encoding the polypeptide sequences of SEQ ID Nos: 2, 11, 12, 24, 25, 26 constitutes a species.

Applicant's arguments in paper No: 13 have been considered but are found not to be persuasive for the following reasons:

1. Restriction of the polypeptides of SEQ ID Nos: 2, 11-12, 24-26 from their encoding polynucleotides is proper because the structure of the polypeptides do not share the same or common property with the encoding DNA sequences.

2. Restriction of the method of group 18, claim 36, from group 1 is proper, because the method of group 18 is an additional use of SEQ ID NO:2. In a national stage application, if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims (see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d)) and after that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).).

Concerning rejoining group 18, claim 36 with group 1 according to *In re Ochiai,* the examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be

fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

3. Restriction of the method of groups 24, 25-29 from group 1 is proper, because the methods of groups 24, 25-29 do not use the polypeptides recited in group 1, and thus do not share the same technical features.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 15-18, 22-23, 34-35 are examined in the instant application, wherein claims 15-18, 22-23, 34-35 are examined only to the extent of the polypeptides of SEQ ID NOs:2 and 11-12. SEQ ID Nos: 24-26 are withdrawn from

consideration, because prior art for species SEQ. ID Nos: 11-12 has been found (see 102 rejection).

Claims 15, 22 seem to be free of prior art and are allowable.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

The specification recites amino acid sequences, for example on pages 5, 11, 20-21, that are not accompanied with sequence identification numbers.

Appropriate correction is required.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 16-18, 23, 35 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 16-18, 23, 35 are drawn to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:11, or SEQ ID NO:12, or a composition comprising said

polypeptide and a method for inducing a cytotoxic T lymphocyte response in vivo, comprising administering said polypeptide.

It is noted that SEQ ID NO:11 and SEQ ID NO:12 are 11 and 10 amino acid fragments, respectively, of the full length polypeptide of SEQ ID NO:2.

Claims 16-18, 23, 35 encompass unrelated sequences with unknown structure, "comprising" 11 or 10 amino acid fragments consisting of SEQ ID NO:11 or SEQ ID NO:12, respectively, which are also comprised within SEQ ID NO:2, and a method of inducing a cytotoxic T cell response using said sequences. In other words, claims 16-18, 23, 35 encompass variants of SEQ ID NO:2, and a method of inducing a cytotoxic T lymphocyte response in vivo using said variants.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not

specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed

correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a polypeptide comprising SEQ ID NO:11 or SEQ ID NO:12, per Lilly by structurally describing a representative number of polypeptides comprising SEQ ID NO:11 or SEQ ID NO:12 or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a polypeptide comprising SEQ ID NO:11 or SEQ ID NO:12 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any polypeptide comprising SEQ ID NO:11 or SEQ ID NO:12 other than the full length CAMEL polypeptide of SEQ ID NO:2, nor does the specification provide any partial structure of such polypeptide comprising SEQ ID NO:11, or SEQ ID NO:12, nor any physical or chemical characteristics of the polypeptide comprising SEQ ID NO:11 or SEQ ID NO:12, other

than the full length CAMEL polypeptide of SEQ ID NO:2, nor any functional characteristics, coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polypeptide of SEQ ID NO:2 comprising SEQ ID NO:11 or SEQ ID NO:12 on page 20, second paragraph, this does not provide a description of a polypeptide comprising SEQ ID NO:11 or SEQ ID NO:12, that would satisfy the standard set out in Enzo.

The specification also fails to describe the polypeptide comprising SEQ ID NO:11 or SEQ ID NO:12 by the test set out in Lilly. The specification describes only a single polypeptide comprising SEQ ID NO:11 or 12. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the polypeptide comprising SEQ ID NO:11 or SEQ ID NO:12, that is required to practice the claimed invention. Since the specification fails to adequately describe the products used to perform the claimed methods of claims 34-35, it also fails to adequately describe the claimed method.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 34-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing a cytotoxic T lymphocyte response in vitro, **does not reasonably provide enablement for a method for**

inducing a cytotoxic T lymphocyte response "in vivo". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 34-35 are drawn to a method for inducing a cytotoxic T lymphocyte response in vivo comprising administering an isolated polypeptide comprising the amino acid sequence of SEQ ISD NO:2, 11 or 12.

The specification discloses that the CAMEL polynucleotide comprising SEQ ID NO:1 encoding SEQ ID NO:2 (or cDNA clone 4H8) is a truncated form of LAGE-1 cDNA known in the art. The specification further discloses that the encoded CAMEL polypeptide (SEQ ID NO:2) is an alternative translation of tumor antigen LAGE-1, and is similar to the alternative translation of NY-ESO-1, except the last 5 amino acids due to an earlier stop codon (p.20, last paragraph bridging p.21, first paragraph).

The specification further discloses that a clone containing the CAMEL cDNA comprising SEQ ID NO:1, when expressed in COS-7 cells, is able to stimulate TNF-alpha release by melanoma-specific CTL 1/29 (Example 1 on p.19). The specification also discloses that SEQ ID Nos:11 and 12 which are the first 11 and 10 amino acids, respectively, of the CAMEL polypeptide comprising SEQ ID NO:2, induce preponderant recognition by CTL 1/29 (p. 20, second paragraph).

The specification contemplates in vivo induction of CTL useful in cancer therapy (p.7, last two paragraphs).

A. One cannot extrapolate the disclosure in the specification to the scope of the claim, because **it is unpredictable that the CAMEL polypeptide comprising SEQ**

ID NO:2, 11 or 12 is capable of inducing specific cytotoxic T lymphocytes in vivo. Kirkin, AF et al, 1998, APMIS 106: 665-679 teach that although the ability to present CTL epitopes *in vitro* recognized by CTLs have been shown for some antigenic epitopes of MAGE-A1, such as EADPTGHSY (same as SEQ ID NO:1 of MAGE-1 in US 5,405940), and SAYGEPRKL, and four epitopes have been identified for MAGE-3, except for only one MAGE-A3 peptide, EVDPIGHLY, none of other identified peptides have been found to have the ability to induce CTLs *in vivo*, or have limited anti-tumor activity (page 666, last paragraph of first column, bridging second column, and second paragraph of second column of p.666, and p.669, second paragraph of second column). Kirkin, AF et al also teach that a review of the melanona- associated antigens belonging to the group of cancer/testis specific antigens, such as MAGE, BAGE, GAGE, PRAME and NY-ESO-1 shows that although they contain several potential HLA binding epitopes, however only two patients have been found to respond to these antigens in vivo, indicating their genuinely low immunogenecity (abstract). In other words, based on the teaching in the art, one would conclude that **the ability to induce CTL lysis *in vitro* does not correlate with in vivo induction of CTLs**. This unpredictability applies as well to the claimed method of in vivo induction of CTL, using CAMEL polypeptide, especially in view that CAMEL is strongly homologous with NY-ESO-1 and that the alternative translated product of NY-ESO-1 differs from the CAMEL polypeptide only in its last 5 amino acids (p. 21, first paragraph). Thus one cannot predict that the CAMEL polypeptide comprising SEQ ID NO:2, 11 or 12 is capable of inducing specific cytotoxic T lymphocytes in vivo.

B. Further, the claims 34-35 read on a method for inducing a cytotoxic T lymphocyte in vivo in patients having cancer burden.

One cannot extrapolate the disclosure in the specification to the scope of the claim, because **it is unpredictable that SEQ ID NO:2, 11 or 12 is capable of inducing specific cytotoxic T lymphocytes in patients having cancer burden, due to immune tolerance.** Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). Similarly, Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). Thus based on the teaching in the art , one cannot predict that a cytotoxic T lymphocyte response could be induced in patients having tumor burden.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the

state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of in vivo induction of cytotoxic T lymphocyte response, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph rejection, claims 16-18, 23, 35 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide **consisting of** SEQ ID NO:11 or SEQ ID NO:12, and a method of inducing a CTL response, using said polypepitde, **does not reasonably provide enablement for an isolated polypeptide "comprising" SEQ ID NO:11 or SEQ ID NO:12,** and a method of inducing a CTL response, using said polypepitde. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 16-18, 23, 35 are drawn to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:11, or SEQ ID NO:12, or a composition comprising said polypeptide and a method for inducing a cytotoxic T lymphocyte response in vivo, comprising administering said polypeptide.

It is noted that SEQ ID NO:11 and SEQ ID NO:12 are 11 and 10 amino acid fragments, respectively, of the full length polypeptide of SEQ ID NO:2.

Claims 16-18, 23, 35 encompass unrelated sequences with unknown structure, provided that they share with SEQ ID NO:2 the 11 or 10 amino acid fragment consisting of SEQ ID NO:11 or SEQ ID NO:12, respectively, and a method of inducing a cytotoxic T lymphocyte response in vivo using said unrelated sequences. In other words, claims 16-18, 23, 35 encompass variants of SEQ ID NO:2, and a method of inducing a cytotoxic T lymphocyte response in vivo using said variants.

The scope of the claims includes numerous structural variants. Applicants have not shown how to make the claimed variants which are capable of functioning or have the biological activity or characteristics of the polypeptide comprising SEQ ID NO:2, as that which is being disclosed.

Thus, the claimed numerous variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions, provided that the change is not in the amino acid sequence fragment consisting of SEQ ID NO:11 or 12. The specification and the claims

do not place any limit on the type of substitution besides conservative substitution, nor the type of insertion or deletion. In addition, the specification and the claims do not place any limit on the number of amino acids that could be substituted or deleted or inserted in the sequences that comprise SEQ ID NO:11 or 12. Thus the scope of the claims includes numerous structural variants. Although the specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide sufficient guidance as to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated.

Further, one cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the claimed variants of SEQ ID NO:2 would have biological activity or characteristics related to that of SEQ ID NO:2. It is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in

any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In addition, since one does not know how to make the claimed polypeptide variants for used in the claimed methods, one cannot perform or make the claimed method.

The specification does not disclose how to make the claimed variants, such that they would the biological activity or characteristics as claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the

United States and was published under Article 21(2) of such treaty in the English language.

Claims 16-18 are rejected under 35 U.S.C. 102(a or e) as being anticipated by Wang RF et al, Genbank Sequence Database (Accession AC 095146), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, and J Immunol, 161: 3596-3606, publicly available on 10/01/98, or by WO9918206-A2, which is from PCT/US98/19609, filed on 21 September 1998, and which has as priority date 08 October 1997 of a CIP US 60/061428.

Claims 16-18 are drawn to a polypeptide "comprising" the amino acid sequence of SEQ ID NO:11 or SEQ ID NO:12.

Wang et al teach an amino acid sequence which is 100% identical to SEQ ID NO:11 and which comprises a sequence that is 100% identical to SEQ ID NO:12, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2003, us-09-807-512-11.rspt, p.1-2).

WO9918206-A2 teaches an amino acid sequence which is 100% identical to SEQ ID NO:11 and which comprises a sequence that is 100% identical to SEQ ID NO:12, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2003, us-09-807-512-11.rag, p.3).

All of the limitations of the claims are met.

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang RF et al, *supra*, or WO9918206-A2, *supra,* in view of Johnstone and Thorpe (Immunochemistry in Practice, 2nd Ed., 1987, Blackwell Scientific Publications, Oxford, pages 49-50).

Claim 23 is drawn to a composition comprising the polypeptide of SEQ ID NO:11 or 12 and a pharmaceutically acceptable carrier.

The teaching of Wang RF et al, or WO9918206-A2 has been set forth above.

Wang RF et al, or WO9918206-A2 however do not teach a composition comprising the amino acid sequence and a pharmaceutically acceptable carrier.

It is noted that a pharmaceutically acceptable carrier could be interpreted as any type of carrier, such as buffer, provided that it is pharmaceutically acceptable.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to put the polypeptide taught by Wang RF et al, or WO9918206-A2 in buffer, such as phosphate buffer saline (PBS), because of the following reasons: 1) Johnstone and Thorpe teach that compositions of antibodies are stored in phosphate buffer saline, which is considered to be an acceptable carrier for storage of antibodies, because Johnstone and Thorpe teach that antibodies could be damaged, even though antibodies are robust proteins, and that antibodies are happiest

in neutral isotonic buffers such as PBS (p.50, first paragraph), and 2) Antibodies are proteins and it was conventional to store proteins in phosphate buffer saline. One of ordinary skill would have been motivated to do so in order to develop compositions suitable for storage.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

PATENT EXAMINER

November 06, 2003